International Journal of Advanced Engineering, Management and Science (IJAEMS)
Peer-Reviewed Journal
ISSN: 2454-1311 | Vol-11, Issue-3; May-Jun, 2025
Journal Home Page: https://ijaems.com/
DOI: https://dx.doi.org/10.22161/ijaems.113.4

Integrative Molecular and Phytotherapeutic Strategies in Alzheimer's Disease: A Review of Advances in Pathogenesis, Genetic Markers, And Natural Drug Design

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Received: 15 Apr 2025; Received in revised form: 08 May 2025; Accepted: 12 May 2025; Available online: 14 May 2025

Abstract *— Alzheimer's Disease (AD) is a complex brain disorder involving memory loss and cognitive decline. This review highlights recent progress in understanding how certain genes and brain pathways contribute to the disease. It also explores the role of plant-based compounds, such as curcumin and silymarin, in reducing brain inflammation and protein buildup. Advances in computer-based drug design and personalized medicine are discussed, along with the ongoing challenges in developing treatments that are both effective and easy for the brain to absorb. A combined approach using genetics, natural therapies, and technology may offer better solutions for managing AD.*

Keywords *— Alzheimer's, Curcumin, Tau Pathology, Computational Modeling, Natural Compounds, Cholinergic Dysfunction, Antioxidants*

I. INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder marked by amyloid-β plaque accumulation, tau hyperphosphorylation, and neuroinflammation, leading to cognitive decline and synaptic dysfunction (Tiwari et al., 2019; Wei et al., 2023). Disruptions in key pathways—such as Wnt/β-catenin, NF-κB, and cholinergic signalling—further contribute to neuronal damage and blood–brain barrier compromise (Wang et al., 2022; Chen et al., 2022; Ding et al., 2022).

Genetic risk factors, particularly APOE4, BIN1, and CR1, have been strongly associated with lipid metabolism defects, immune dysregulation, and cerebrovascular pathology in AD (Martens et al., 2023; Jansen et al., 2022). Phytotherapeutic agents like curcumin, silymarin, and quercetin exhibit antioxidant and anti-amyloid effects, making them promising candidates for multi-target interventions (Koul et al., 2023; Shah-abadi et al., 2023; Swaraz et al., 2021).This review focuses on the integration of molecular insights, genetic profiling, and phytochemical therapeutics, highlighting novel directions in natural drug design and computational modeling for AD management.

II. PATHOGENESIS AND MOLECULAR BASIS

The foundational work by Tiwari et al. (2019) emphasizes that Aβ plaque deposition and tau hyperphosphorylation drive neuronal dysfunction, particularly in the cortical and limbic brain regions. These pathological formations are compounded by microglial activation that initiates innate immune responses, exacerbating synaptic loss and neurodegeneration. Zhang et al. (2024) further expanded on this by demonstrating that complement

protein C1qA, activated by microglia, contributes to aberrant synaptic pruning and cognitive decline in the FAD4T mouse model. Wei et al. (2023) provided a novel insight into epigenetic modulation where H3K18 lactylation in senescent microglia activated the NFκB pathway, increasing the production of inflammatory cytokines IL-6 and IL-8, thereby promoting aging-related neurodegeneration.

The cholinergic hypothesis also plays a significant role. Chen et al. (2022) observed that abnormalities in acetylcholine (ACh) signaling disrupt tau phosphorylation, increase inflammation, and promote neuronal apoptosis. Their findings validate why current treatments target cholinesterase inhibition. Additionally, the work of Wang et al. (2022) illustrates how Wnt/β-catenin signaling disruption impairs the blood-brain barrier (BBB), reducing tight junction protein expression and facilitating Aβ infiltration, a phenomenon observed in both human and animal models of AD.

III. GENETIC RISK FACTORS AND COMPUTATIONAL INSIGHTS

Genetics play a pivotal role in AD, particularly the Apolipoprotein E (APOE) gene. Martens et al. (2023) introduced the "ApoE Cascade Hypothesis," proposing that the biochemical properties of APOE4 trigger lipid metabolism dysfunction, inflammation, and cerebrovascular impairment. This cascade not only accelerates Aβ and tau pathologies but also contributes to early-onset neurodegeneration. Jansen et al. (2022), through genome-wide meta-analysis of cerebrospinal fluid (CSF) biomarkers, discovered that loci such as CR1 and BIN1—alongside APOE—significantly correlate with AD pathophysiology.

Bourquard et al. (2023) employed a machine learning-based framework known as EAML to identify sex-specific variants influencing AD. Their study revealed that male and female AD patients have distinct genetic pathways, including stress response and cell-cycle regulation, emphasizing the need for personalized treatment strategies. In silico studies have also proven effective in drug discovery. Arfat et al. (2023) successfully designed multiepitope peptide vaccines targeting MAPK protein in zebrafish models, offering a template for future vaccine-based approaches. Shaji et al. (2023) used fragment molecular orbital methods to reveal how quercetin derivatives interact with APOE4, suggesting plant-based inhibitors as viable therapeutic candidates.

IV. PHYTOCHEMICALS AND NATURAL PRODUCT-BASED INTERVENTIONS

Plant-derived bioactives have gained recognition as multi-target therapeutic agents. Koul et al. (2023) identified 55 plants with neuroprotective potential, rich in compounds like galantamine, curcumin, and silymarin that possess antioxidant, anti-amyloidogenic, and anticholinesterase properties. Swaraz et al. (2021) studied Blumea laciniata, demonstrating strong in vitro and in silico enzyme inhibition activity with compounds like rosmarinic acid, rutin, and kaempferol showing high binding affinity and no observed toxicity in diabetic models.

Azam et al. (2014) evaluated ginger components via docking studies and confirmed their binding efficacy against AChE, COX-2, and NMDA receptors. Shah-abadi et al. (2023) compared natural and synthetic ligands, finding that silymarin, quercetin, and rosuvastatin are effective inhibitors of AChE and P-glycoprotein. Their results support the use of phytochemicals in enhancing Aβ clearance, especially when used in combination with nanoparticles to bypass the BBB.

V. TRADITIONAL AND ADJUNCT THERAPEUTICS

Traditional Chinese Medicine (TCM) offers an alternative paradigm by targeting multiple signaling axes involved in AD progression. Ding et al. (2022) reviewed how herbal formulations modulate pathways like NFκB, PI3K/Akt/mTOR, and JAK/STAT, which are associated with neuroinflammation, autophagy, and protein degradation. Many herbs studied also activate antioxidant defenses through Nrf2 signaling, offering synergistic effects with modern drugs.

Nagu et al. (2022) outlined the importance of Wnt signaling in neurogenesis and cognitive function. Disruptions in this pathway due to Aβ accumulation decrease β-catenin levels and increase GSK3β activity. Their analysis suggests compounds like huperzine A, curcumin, and cannabidiol as potent Wnt modulators

capable of restoring synaptic integrity. These adjunct therapies can be integrated into personalized medicine approaches for better disease management.

VI. CHALLENGES AND FUTURE DIRECTIONS

Despite remarkable progress in molecular research and therapeutic discovery, several challenges impede the effective treatment of Alzheimer's Disease (AD). A critical barrier lies in the pharmacokinetics of promising phytochemicals like curcumin and silymarin, which display poor bioavailability and limited blood–brain barrier permeability (Shah-abadi et al., 2023; Koul et al., 2023). Nanoparticle-mediated delivery and green nanotechnology approaches are under investigation but require rigorous clinical validation.

Furthermore, a translational disconnect persists between animal models and human clinical outcomes. Compounds that demonstrate efficacy in silico or in murine models frequently fail in clinical trials due to inter-individual variability and disease heterogeneity (Breijyeh & Karaman, 2020). The limited inclusion of sex-specific genetic differences in drug response further complicates the personalization of therapy (Bourquard et al., 2023).

Advanced computational tools like machine learning frameworks (e.g., EAML) have highlighted the importance of sex-stratified analyses and variant prioritization, yet such methodologies are not mainstream in drug development (Bourquard et al., 2023). The integration of such insights into precision medicine protocols is a necessary future direction.

Moreover, while APOE4, Wnt signaling, and NFκB pathways have emerged as crucial molecular targets, the lack of combination therapies that simultaneously address inflammation, protein aggregation, and cognitive symptoms remains a key gap. Effective clinical translation will require synergy between AI-based drug discovery, biomarker-guided trials, and adaptive therapeutic frameworks.

VII. CONCLUSION

Alzheimer's Disease continues to pose a multifactorial clinical and public health challenge, driven by intricate interactions among genetic, molecular, and environmental components. This review has consolidated emerging evidence on APOE cascade dynamics, cholinergic dysfunction, Wnt pathway modulation, and the promise of phytochemical therapeutics. Recent advances in computational modeling, machine learning-based genetic analysis, and nanotechnology offer a renewed hope for innovative treatments.

Future strategies should focus on enhancing drug delivery systems, embracing personalized treatment protocols, and developing multitargeted therapies that span across neuroinflammatory, amyloidogenic, and synaptic repair pathways. Collaboration between neuroscientists, pharmacologists, and computational biologists will be pivotal in converting research insights into tangible clinical progress against AD.

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